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PERSPECTIVES IN RENAL MEDICINE

Living unrelated donor kidney transplantation

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Living unrelated donor kidney transplantation.

Background. Living unrelated donors remain an underutilized resource, despite their high graft survival rates. In this article, we updated the long-term results of more than 2500 living unrelated donor transplants performed in the United States.

Methods. Between 1987 and 1998, 1765 spouse, 986 living unrelated, 27,535 living related, and 86,953 cadaver donor grafts were reported to the United Network for Organ Sharing Kidney Registry. Kaplan–Meier curves compared graft survival rates in stratified analyses, and a log-linear analysis adjusted donor-specific outcomes for the effects of 24 other transplant factors.

Results. The long-term survival rates for both spouse and living unrelated transplants were essentially the same (5-year graft survivals of 75 and 72% and half-lives of 14 and 13 years, respectively). The results were similar to that for parent donor grafts (5-year graft survival = 74% and half-life = 12 years) and were significantly ($P = 0.003$) better than cadaver donor grafts (5-year graft survival = 62% and half-life = 9 years). After adjusting for the presence of transplant factors known to influence survival rates, recipients of living unrelated donor kidney transplants still had superior outcomes compared with cadaver transplants.

Conclusions. Living unrelated kidney donors represent the fastest growing donor source in the United States and provide excellent long-term results. Encouraging spouses to donate could remove nearly 15% of the patients from the UNOS waiting list, effectively increasing the number of available cadaveric organs.

Five years ago, we summarized data on kidney grafts from spouses and other living unrelated donors into patients with end-stage renal disease, as reported to the United Network for Organ Sharing (UNOS) Transplant Registry [1]. Despite poor human lymphocyte antigen (HLA) matching, these unrelated donor transplants exhibited high graft and patient survival rates similar to outcomes of parent donor kidney grafts and superior to outcomes of cadaver donor kidney grafts. The excellent survival rates were attributed to the fact that kidneys from living donors were uniformly healthy.

Even then, evidence of unexpectedly high graft survival rates in living unrelated donor transplants had been mounting for years [2–8]. For example, two Korean centers with the largest numbers of such cases at the time reported that their five-year graft survival rates for living unrelated donor transplants were near 80%, indistinguishable from their living related donor counterparts [3, 7]. Brain death was not legally accepted in Korea, so except for a few non–heart-beating cadaver donor cases, spouses and other living unrelated individuals were the only organ source when relatives were unavailable. In countries that have established brain death laws, the acute shortage of cadaveric organs has spurred the growth of living unrelated kidney transplants as well.

Despite the evidence for excellent outcomes, living unrelated donors remain an underutilized resource. In particular, only a small fraction of the estimated 6000 potential spouse donors per year have been actual donors in the United States [1, 9]. Besides issues of coercion, morbidity, and mortality [10], another impediment to living unrelated donation has been the argument that less restrictive recipient selection criteria coupled with greater HLA incompatibility would result in lower success rates [11]. In contrast, each successive summary has shown one-year graft survival rates holding at 90% as reviewed by Cecka [12].

In this article, we re-examined the results of living unrelated donor kidney transplants performed in the United States and concentrated on long-term and joint (that is, combinations of transplant factors) outcomes, presenting results of more than 2500 living unrelated donor transplants reported to the UNOS Kidney Registry through 1998. Graft survival at five years after transplantation (five-year GS) and graft half-lives (HL; times in years at which one half of grafts surviving beyond 1 year fail) were used as long-term measures. Overall, the current report provides strong evidence of excellent long-term graft outcomes using living unrelated donors regardless of the effects of transplant cofactors.

Key words: graft survival, end-stage renal disease, organ sharing, renal transplantation.

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METHODS

Study population and variable selection

Between October 1987 and December 1998, data on 117,239 renal transplants from 244 centers were reported to the UNOS Transplant Registry with follow-up through October 1999. Grafts from 1765 spouses, 986 other living unrelated donors, 6855 parents, 4859 HLA-identical siblings, 8787 other siblings, plus 7034 other living related, and 86,953 cadaver donors were included for study. In a secondary analysis of adjusted donor-relationship outcomes among adult (≥21-year-old) recipients, it was necessary to partition post-transplant time into consecutive intervals and to analyze subsets of patients entering each interval. The initial subset included 98,652 adult transplants that functioned beyond hospital discharge, and the second set consisted of 87,981 grafts that functioned beyond one year.

Survival time and indicators for one-year and five-year graft function, as well as the graft's function status at the patient's last follow-up time were analyzed as outcome variables. When necessary, the last reported serum creatinine value was used to impute one- and five-year graft function for censored patients [13, 14]. Indicators for the donor's relationship to the recipient as well as 24 other transplant factors (**Appendix**) were selected as explanatory variables for stratification and multivariable analysis. Less than 5% of values were missing for any covariate. When missing, data were replaced with mode values for categorical variables and mean values for continuous variables. Continuous variables were further categorized to obviate linearity assumptions.

Statistical methods

Kaplan–Meier curves and log-rank tests were used to describe and compare the graft survival rates in stratified univariate analyses. All *P* values were two sided. Patients who died were considered to have had graft failure. Long-term survival rates were re-expressed as graft HLs, that is, times in years at which one half of grafts surviving beyond one-year post-transplantation fail [15].

A secondary analysis (used to adjust donor-relationship effects for other transplant factors) was based on a method pioneered by Mickey [16, 17]. Donor scores were estimated using a log-linear analysis of partial associations of outcome, and reiterated on each post-transplant period [18]. (The partial associations of outcome were based on scores from the cofactors and centers given in **Appendix**. Readers interested in the details should contact the authors.) Adjusted probabilities of graft survival for different donor sources were estimated according to the formula: $p = 1/(1 + \exp(-(w_0 + w)))$, where exp() denotes the exponential function e; w_0 represents baseline values 2.1218 (corresponding to 89.3% graft survival at one year given hospital discharge) and 1.2425 (corresponding to 77.6% graft survival at five years given 1-year survival), and w is the score corresponding to the categories and terms outlined in Table 1.

The adjusted values represent the survival that would result if only donor relationship was operational and all other factors were assumed to be fixed with no variation. Overall, the donor relationship accounted for 26 and 4% of the variation in one- and five-year outcomes, respectively. In this part of the analysis, tests of significance were done using the chi-square method.

Table 1. Numeric scores (w) for adjusting graft survival probabilities according to type of donor

Categories	1-year	5-year
Parent	0.2544	−0.2786
Sibling	0.2918	0.2350
Other related	−0.2002	0.2056
Spouse	0.0158	−0.0214
Living unrelated	0.2314	0.1604
Cadaver	−0.5934	−0.3008

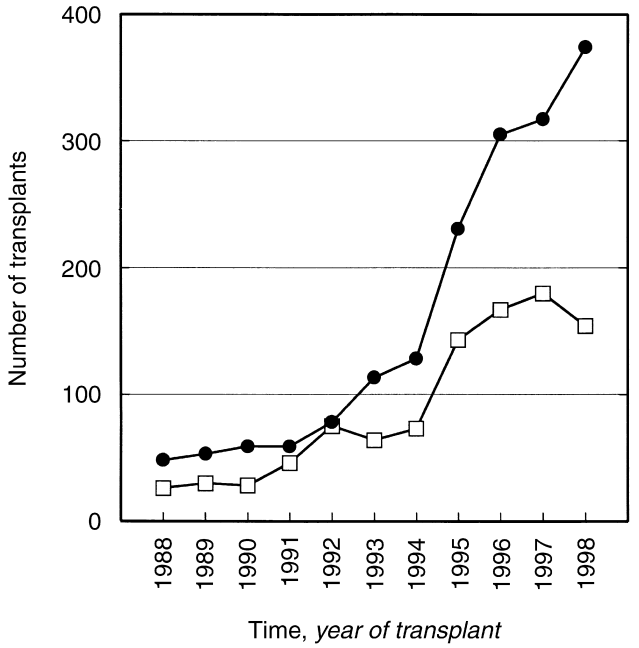

Fig. 1. Growing use of spouse (●) and other living unrelated (□) kidney donors at United States transplant centers.

RESULTS

Spouse and other living unrelated donor grafts have increased significantly since 1994 (Fig. 1). After 1995, the numbers of spouse transplants rose by nearly 20% each year so that in 1998 alone, nearly 400 spouse transplants were reported to UNOS. During this period, the numbers of other living unrelated donor transplants appeared to stabilize at around 160 per year.

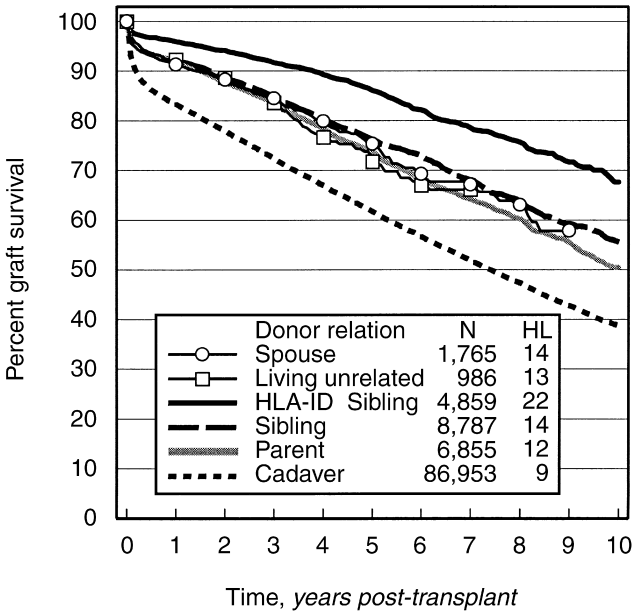

Fig. 2. Graft survival rates for kidney transplants performed between October 1987 and December 1998 according to the donor source.

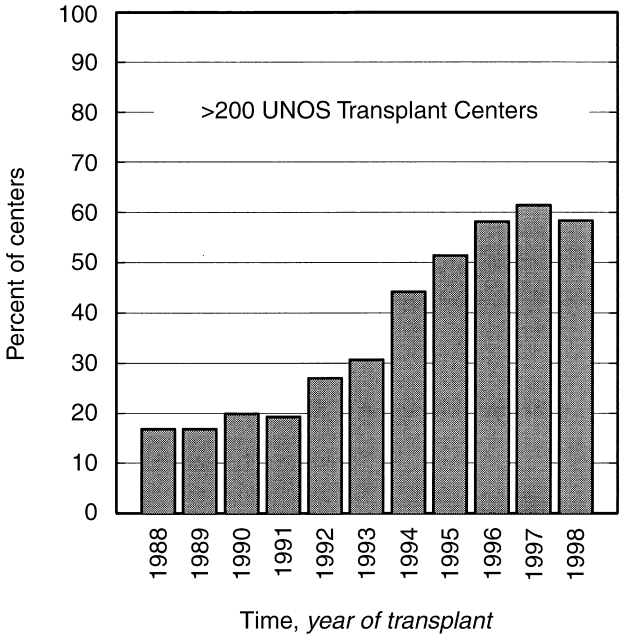

Fig. 3. Annual percentage of U.S. transplant centers reporting at least one living unrelated donor transplant during each year.

Grafts from HLA-identical siblings (genetically matched for all of the HLA loci) and from other siblings (with 2.7 average mismatched antigens at the HLA-A, -B, and -DR loci) had the highest survival rates (five-year GS = 86 and 75%, and HL = 22 and 14 years, respectively; Fig. 2). Grafts from cadaver donors (3.4 average mismatched HLA antigens) had the lowest survival rates (five-year GS = 62% and HL = 9 years), and grafts from parent donors (one HLA-haplotype matched) had intermediate survival rates (five-year GS = 74% and HL = 12 years). The survival rates for both spouse and other living unrelated transplants were essentially the same (five-year GS of 75 and 72%, and HL of 14 and 13 years, respectively, $P = 0.33$) and similar to that for parent-donor grafts. Living unrelated donor grafts exhibited significantly better outcomes ($P = 0.003$) than cadaver donor grafts, despite the fact that they had a higher average number of mismatched HLA antigens (4.2 mismatches).

The number of U.S. centers performing living unrelated transplants each year has also steadily increased over the ten year period of this study (Fig. 3). Prior to 1992, fewer than 20% of all UNOS centers reported any kidney transplants with living unrelated donors. More recently (1996 to 1998), nearly 60% (146 of the 244 centers) of UNOS centers were transplanting kidneys from living unrelated donors. Most (140) centers transplanted between 10 and 30 living unrelated grafts. Over the course of the study, only 31 of the 244 centers reported no transplants from living unrelated donors. This fact and the results of the multifactor analysis (Fig. 4) confirm that center-specific effects did not account for the high survival rates of living unrelated kidney transplants.

The results of secondary analyses adjusting the donor-relationship survival rates for the effects of center and 24 transplant factors are shown in Figure 4. (Note that since the rates were adjusted for the inherent grades of HLA match as part of the multifactor analysis, all donor types, including sibling donors, were displayed using one category per donor type.) Figure 4A depicts the probability of grafts surviving to one year after transplantation given that the recipient was discharged from the hospital, and the right panel shows the survival probabilities to five years provided the recipient had a functioning graft at one year. Bars represent 95% confidence intervals for donor-specific categorical rates. All recipients of living donor transplants enjoyed superior one-year graft survival rates compared with cadaveric transplants (82%), and the adjusted one-year graft survival rates for spouse (90%) and living unrelated transplants (91%) were similar to rates for living related donor transplants (92% for parent and sibling donor grafts).

At five years (Fig. 4B), survival rates for patients receiving sibling, spouse, or living unrelated donor kidneys were approximately equal (approximately 80%) and were well above those for parent and cadaver donor types that yielded equally poor long-term values (approximately 72%). The multifactorial analyses demonstrated that spouse and living unrelated donor kidney transplants generally had superior short- and long-term outcomes, regardless of the presence of other transplant

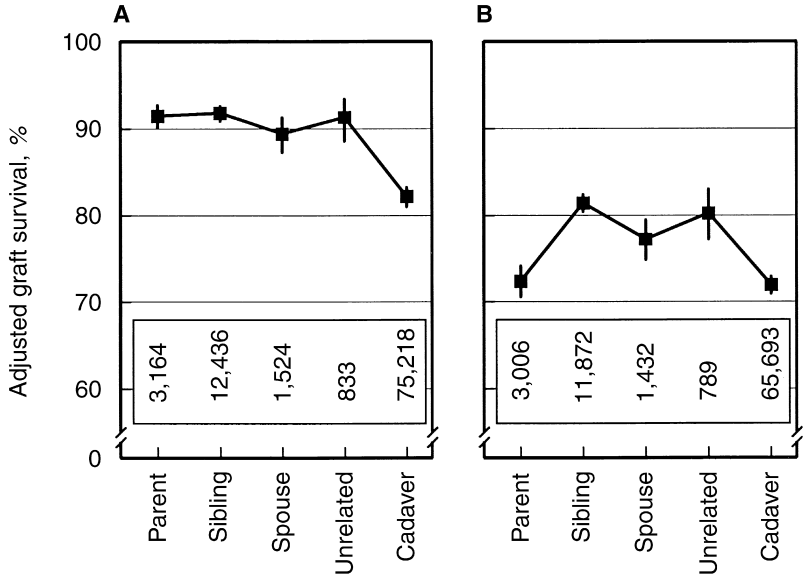

Fig. 4. Adjusted one- (*A*) and five (*B*)-year graft survival rates according to donor source (the text discussed the details of the methods; $P < 0.0001$).

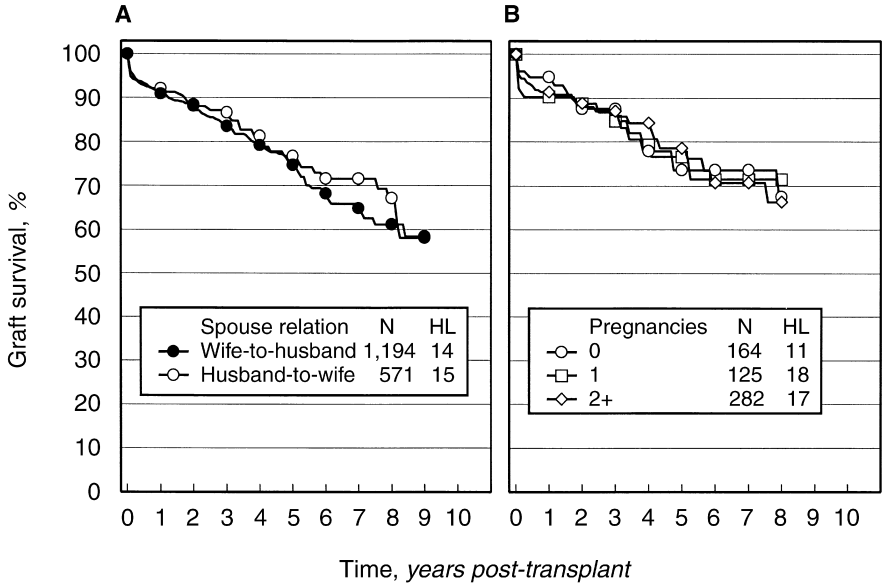

Fig. 5. Graft survival of wife-to-husband and husband-to-wife kidney transplants (*A*; $P < 0.050$) and husband-to-wife transplants according to the wife's history of pregnancies (*B*; $P < 0.094$).

factors known to influence survival rates. Specific data, presented next, confirmed this observation by comparing outcomes for living unrelated donor transplants stratified by several covariates (recipient's sex, sensitization, and number of HLA mismatches).

Regarding the spouse's relationship, graft survival rates were not significantly different ($P = 0.50$) when comparing wife-to-husband or husband-to-wife combinations (Fig. 5), but twice as many wives as husbands were donors. Some husbands may have been excluded as donors by a positive cross-match test since wives may have been immunized to their husband's HLA antigens by pregnancy. However, as shown at the right in Figure 5, the graft survival rates among wives who received their husbands kidney were similar ($P = 0.94$) to those of wife-to-husband transplants, regardless of the number of past pregnancies. Thus, even multiparous wives exhibited survival rates exceeding the rates for cadaveric renal transplants.

The effects of sensitization variables on all (spouses plus other) living unrelated donor kidney transplants were compared and contrasted with effects on cadaver grafts in Figure 6. The graft survival rate of repeat transplants from living unrelated donors was significantly (Fig. 6A; $P < 0.0001$) lower than the rate in primary living unrelated donor grafts (five-year GS of 75 vs. 64% and

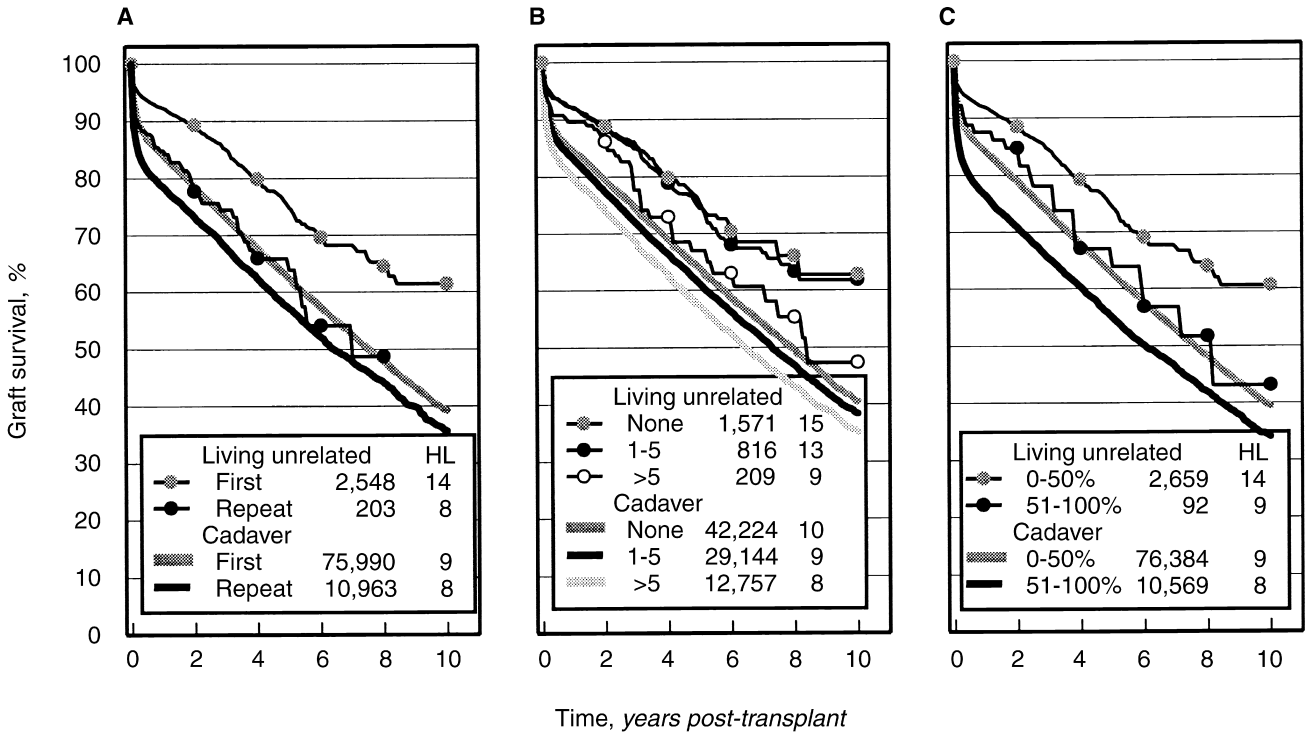

Fig. 6. Comparison of living unrelated and cadaver donor transplants when the recipient may have been immunized by a previous transplant failure (*A*), pretransplant blood transfusions (*B*), or had panel-reactive antibodies (*C*).

HL of 14 vs. 8 for first vs. repeat grafts, respectively). The magnitudes of the difference in rates between first and repeat living unrelated donor kidney transplants were greater than corresponding differences found in cadaver donor transplants. Likewise, the effects of pretransplant transfusions and anti-HLA antibodies (Fig. 6 B and C) were more pronounced (but statistically less significant because of the smaller number of cases) among living unrelated transplants than cadaver transplants. In both living unrelated and cadaver donor kidney transplants, patients with six or more transfusions or high levels of panel reactive antibodies (PRA $>$ 50%) demonstrated poorer long-term outcomes compared with recipients with few transfusions (0 to 5) or low PRA (0 to 50%). The vast majority of living unrelated donor kidneys were transplanted to primary (93%) and unsensitized (97%) recipients, indicative of careful selection and screening processes.

Increasing numbers of HLA-A, -B, and -DR loci mismatches did not significantly ($P = 0.50$) lower graft survival rates among living unrelated donor kidney transplant recipients (Fig. 7A). There was a tendency for well-matched living unrelated donor kidney transplants to have better survival, but because of small numbers of such cases, no ordered trends were apparent such as the highly significant ($P < 0.0001$) hierarchical effects of HLA found among cadaver transplants. However, the survival rates of even the poorest HLA-mismatched category (5 to 6 mismatches) of living unrelated transplants were better than rates for cadaver transplants with all levels of HLA mismatch except perfectly matched cases, where rates were equal.

The effects of donor type (living unrelated vs. cadaver) and HLA mismatch on delayed graft function (defined as the percentage of hospital-discharged recipients whose grafts were first-day anuric or who required supplemental dialysis during the first-week post-transplant) and first-year rejection episodes are shown in Figure 7B. On average, 7% of living unrelated donor grafts and 24% of cadaveric grafts exhibited delayed graft function ($P <$ 0.0001). Modest increases in the percents of delayed graft function among cadaver (a 3% point increase that was highly statistically significant owing to the large number of cases) and living unrelated (a nonsignificant 7% point increase) donor transplants were associated with zero versus some HLA mismatches. Finally, increasing numbers of HLA mismatches significantly ($P = 0.001$) raised the chance of first-year rejection episodes in living unrelated transplants. From 0 to 6 HLA mismatches, first-year rejection episodes increased steadily from 11 to 35% in living unrelated donor kidney transplants. This approximately 20% point increase was similar to the rate of increase of rejection seen in cadaver donor transplants.

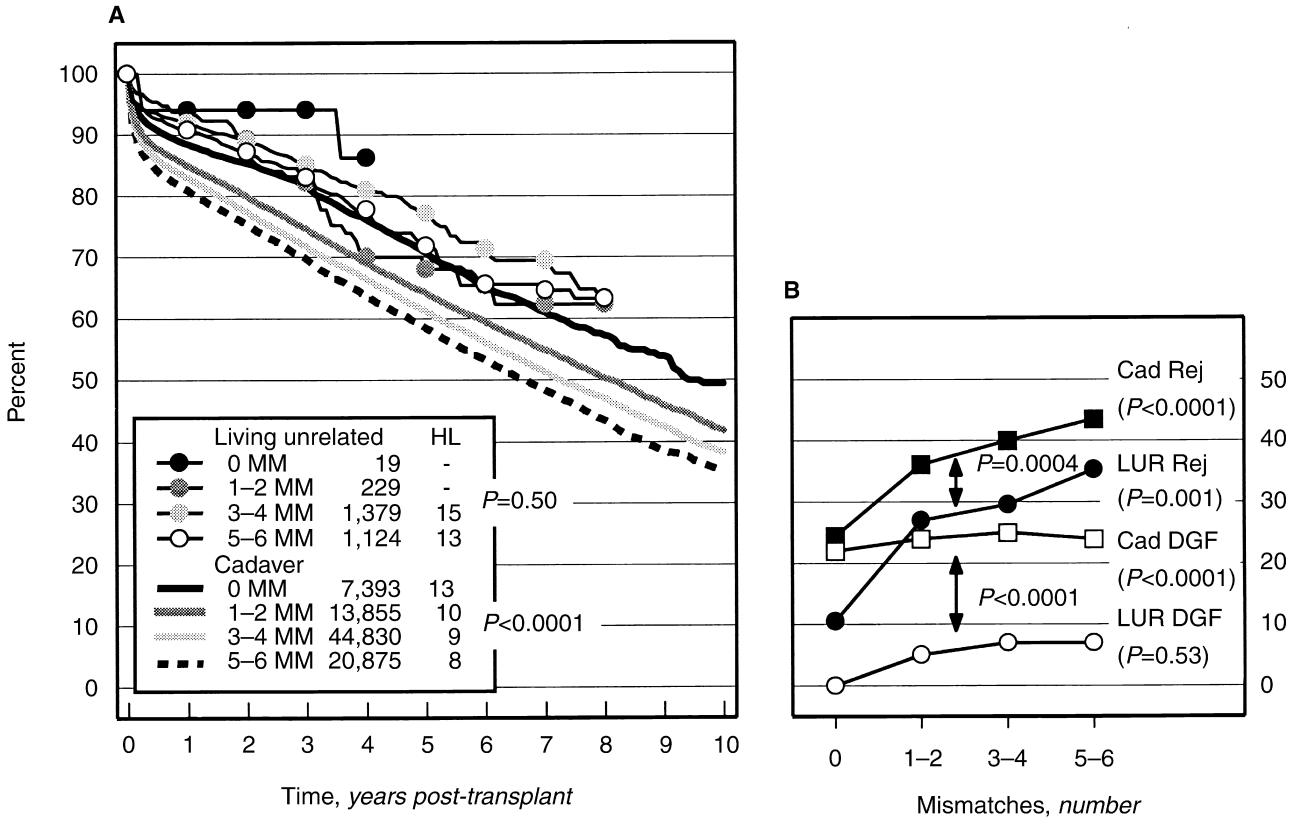

Fig. 7. Effect of HLA mismatches on graft survival (*A*) and delayed graft function and rejection (*B*) of living unrelated (LUR) and cadaver (Cad) donor kidney transplants. Note that only 9% of living unrelated donor transplants had fewer than 3 HLA-A, -B, -DR antigens mismatched compared with 24% of cadaver donor grafts, indicating no selection of living unrelated donors according to HLA compatibility.

DISCUSSION

The transplant literature remains overwhelmingly positive regarding the use of living kidney donors. As illustrated in Figures 1 and 4, the first choice for a living donor is still the patient's sibling and, preferably, an HLA-identical sibling. When siblings and other histocompatible related donors are not available, kidneys from living unrelated donors provide a viable alternative. Worldwide, recent single-center studies have noted high graft survival rates for recipients of living unrelated donor kidneys coupled with very low mortality and morbidity rates for the donors themselves [19–27]. For example, the University of Wisconsin reported five- and ten-year graft survival rates of 82 and 56%, respectively, in their series of 150 unrelated donor transplants dating back to 1981 [19]. In their long-term experience, only one donor died from causes unrelated to the donation, and 17% of 681 living donors developed postoperative complications. The risk of death after donor nephrectomy has been estimated to be 0.03% [28], and the risk of major complications has been calculated to be 0.23% [29]. The most frequent (>1%) complications have been pneumonia, atelectasis, infection (urinary tract and wound), and pneumothorax [30]. Although it is important to be cognizant of the potential risks of the donor surgery, many of the studies that identified these levels of risk include very historical cases. More recent evaluations suggest that the risks today are probably much lower [29, 31]. There is no evidence that living unrelated and related donors experience different risks.

The current results from more than 200 U.S. transplant centers demonstrate that kidney grafts from living unrelated donors continue to have excellent long-term survival rates despite a high degree of HLA incompatibility and that this result is independent of the effects of other transplantation factors (Fig. 4). After adjusting for the effects of center and 24 transplant factors, living unrelated donors exhibited short- and long-term graft outcomes similar to values of sibling donor transplants. At one-year post-transplantation, all living donor types exhibited significantly improved adjusted graft survival rates compared with cadaveric kidney transplants; however, the five-year gs of living unrelated and sibling donor transplants continued to be good, but the parent donor recipients fared much worse and, in fact, had long-term survival rates similar to cadaver kidney recipients. A full explanation for the poor survival of parental transplants is wanting. We suggest that as a consequence of selecting only adult recipients for the multifactorial study, the

parent donors were uniformly older (70% > age 50 years), and therefore, their results remained confounded by the known detrimental effects of old age despite a donor age adjustment.

There was no indication that HLA compatibility played a role in selecting unrelated donor-recipient pairs. However, the data suggest that recipients of living unrelated donor transplants have been carefully selected because few were sensitized or retransplanted. Whether this represents a deliberate avoidance of patients with established immune risk factors or reflects the stringent use of sensitive crossmatch tests or both is not clear. The presence of immunizing factors (for example, more HLA mismatches, repeat transplantations, transfusions, and high levels of antibody) lowered survival rates for living unrelated donor kidney grafts, but the short- and long-term graft survival rates were still better than or equal to those for cadaver transplants in patients without immunizing factors (Figs. 6 and 7).

The stratified analysis measuring the effects of HLA mismatches on living unrelated donor kidney grafts (Fig. 7) did not support the suggestion by Opelz that the transplantation of kidneys from unrelated live donors should be done more selectively so that poor HLA matches can be avoided [11]. In this study, recipients of living unrelated donor kidneys with five to six HLA mismatches had success rates equal to recipients of cadaver kidneys with no HLA mismatches. Our results support the notion that kidneys from living donors are relatively undamaged compared with cadaver donor grafts whose nephron function has been compromised by processes associated with death [1]. In our previous study, when cadaver donor transplants were stratified by the presence and absence of delayed graft function (a surrogate marker of nephron damage), those "absent" cases survived long-term with rates comparable to living donor transplants [1]. In our current study, living unrelated grafts exhibited very low rates of delayed graft function (7%) compared with cadaveric transplants (24%), regardless of histocompatibility (Fig. 7).

Notwithstanding the excellent results, living unrelated donors, particularly spouses, have not reached their full potential as a resource. Among 43,000 patients waiting for a kidney transplant in the United States, as many as 6000 potential spouse donors could be available. This projection is based on a waiting list composed of 95% adults, 50% of whom are married, 60% of whom have an ABO-compatible spouse, and a 50% dropout rate following initial screening for other reasons. If the 6000 potential spouse donors became actual donors, the U.S. waiting list could be reduced by 15%, and the number of available cadaver kidneys would effectively increase for those patients who did not have an alternative donor source. Clearly, the 1765 total accrued spouse transplants and the current rate of 374 spouse transplants per year fall far short of this potential.

Aside from the risks of surgery, the donation process itself may discourage some potential donors who would experience economic hardships as a result of the significant recovery time from the donor surgery. UNOS recently authorized employees up to four weeks of paid leave to cover an absence that results from organ donation, a move designed to reduce any economic disincentive to donation. U.S. government employees will receive a similar benefit based on the Organ Donor Leave Act, which was signed into law in September 1999. The growing use of laparoscopic surgery for the donor nephrectomy also promises to reduce substantially the donors' recovery times [32], providing a more rapid return to normal activities.

However, impediments also seem to be raised by the medical community fearing inferior outcome and possible circumstances of coercion more often than from patients or their families. One survey showed that more than 99% of spouse donors would advise other spouses to donate, and, in general, 82 to 96% of living donors said they would do it again if they could [9, 31, 33]. The fact that the donor reaps benefits as well as the recipient should make spouses the first consideration for kidney donation.

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Appendix. The levels and the computed numerical scores of the transplantation factors used in the multivariable analyses shown in Figure 4

Factor	1-year	5-year
1. Center average	1.0524	0.8475
2. Number of previous transplants		
0	0.1848	0.0614
1	0.0468	0.0452
>1	−0.2316	−0.1066
3. Recipient sex		
Male	−0.0614	−0.1838
Female	0.0614	0.1838
4. Recipient race		
Caucasian	−0.1674	−0.0100
Black	−0.2652	−0.6120
Asian	0.3588	0.3896
Other	0.0736	0.2324
5. Recipient age *years*		
21–25	0.1288	−0.2162
26–45	0.1094	0.0314
46–60	−0.0122	0.1040
>60	−0.2260	0.0810
6. Recipient body mass kg/m^2		
5–14	−0.1804	−0.0770
15–28	0.1066	−0.1368
>28	0.0738	−0.0598
7. Recipient pre-transplant medical status		
Full work	0.2406	0.1514
Part work	−0.0400	−0.0252
Homebound	−0.0304	−0.1298
Hospitalized	−0.1702	0.0034

(continued)

Appendix. (continued)

Factor	1-year	5-year
8. Original disease		
Other	0.0086	−0.0340
Systemic	−0.0818	−0.1990
Inherited	0.0732	0.2330
9. Pre-transplant pregnancies (females)		
0	0.0840	0.0520
1	0.0866	−0.0042
2	0.0034	0.0366
3	−0.0702	−0.0310
>3	−0.1018	−0.0532
10. Pre-transplant transfusions		
0	0.0226	0.0564
1–5	0.0450	−0.0208
6–10	0.0378	−0.0098
>10	−0.0756	−0.1370
Not stated	−0.0298	0.1112
11. Peak panel reactive antibody %		
0	0.1840	0.0522
1–40	0.1308	0.0646
41–80	−0.0474	−0.0318
81–100	−0.2676	−0.0850
12. Dialysis pre-transplant		
≤2 years	0.0478	0.0662
>2 years	−0.0478	−0.0662
13. Donor sex		
Male	0.0948	0.0932
Female	−0.0948	−0.0932
14. Donor race		
Caucasian	0.0628	0.0348
Black	−0.1262	−0.1458
Other	0.0634	0.1110
15. Donor age *years*		
0–3	−0.1354	0.2718
4–15	0.0282	0.2404
16–30	0.2624	0.2510
31–50	0.0858	−0.1086
>50	−0.2410	−0.6550
16. Cold ischemia time *hours*		
0–12	0.1010	0.1212
13–36	0.0298	−0.0120
>36	−0.1308	−0.1092
17. Cause of donor death		
Trauma	0.1374	0.2182
Non-trauma	−0.1374	−0.2182
18. Donor CMV status		
Negative	0.1024	0.0800
Positive	−0.1024	−0.0800
19. Year of transplant		
88–90	−0.3588	−0.1362
91–93	−0.0496	0.0250
94–95	0.1176	0.1112
96–98	0.2906	—
20. HLA-AB mismatches		
0	0.2318	0.2440
1	0.0676	0.0256
2	−0.0172	−0.0682
3	−0.0918	−0.0704
4	−0.1902	−0.1310
21. HLA-DR mismatches		
0	0.1810	0.0620
1	−0.0290	−0.0034
2	−0.1518	−0.0586
22. Ancillary positive crossmatch		
No	0.0612	0.0092
Yes	−0.0612	−0.0092
23. Induction with ALG/OKT3		
No	0.0150	0.0326
Yes	−0.0150	−0.0326
24. Multi-organ transplant		
Kidney	0.0760	−0.2802
+Liver	−0.2638	0.0916
+Pancreas	0.1880	0.1886

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